Remarks

I. Rejection of Claims 22-24 and 26-28 under 35 U.S.C. §112, Second Paragraph.

The Examiner rejected claims 22-24 and 26-28 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner has asserted the following specific deficiencies in the claims:

> Claims 22-24 depend from claim 21. However, claim 21 has been cancelled.
> Claims 26-28 depend from claim 25. However, claim 25 has been cancelled.
> Therefore, claims 22-24 and 26-28 are indefinite because they depend on cancelled claims. (Final Office action, dated 20 April 2005, page 7.)

Applicants thank the Examiner for the Examiner's attention to the language of the claims. Claims 22-24 and 26-28 are, respectively, amended herein to contain the limitations of the independent claims 21 and 25. Accordingly, the claims no longer depend on canceled claims.

In view of the above amendments, applicants submit that the boundaries of the claims are capable of being understood by one of ordinary skill in the art. Therefore, applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, second paragraph, be withdrawn.

II. Addressing the Examiner's Rejection of Claims 1-20 under 35 U.S.C. §112, First Paragraph.

The Examiner maintained the rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, asserting that the specification, "while being enabling for methods of reducing the size of a tumor by the intratumoral injection of Ad5 vector disclosed as dl922/947, dl1107 or pm 928, does not reasonably provide enablement for the full scope of the claims." (Office action, dated 20 April 2005, page 2). The Examiner has noted that this rejection was withdrawn relative to claims 21-28 "as claims 21 and 25 have been cancelled" (Office action, dated 20 April 2005, page 8). However, as discussed above applicants have amended pending claims 22-24 and 26-28 to include the limitations of

the independent claims from which they originally depended. The following arguments regarding the scope of enablement apply to all pending claims, i.e., claims 1-20, 22-24 and 26-28.

If the Examiner chooses to maintain the rejection, applicants respectfully request clarification by the Examiner of the rejection of claims 1-20 under 35 U.S.C. §112, first paragraph. For the following reasons it appears to applicants that the focus of this rejection has become a moving target.

In the first Office action, dated 15 September 2000, Examiner E. Sorbello (the first Examiner in this case) summarized the rejection of claims 1-24 under 35 U.S.C. §112, first paragraph as follows:

> The specification lacks guidance as to the breadth of the claims regarding the mutant adenovirus of the instant invention, and its ultimate functioning in an *in vivo* method of (a) substantially and selectively killing dividing cells, (b) substantially killing less quiescent cells and (c) a method for controlling angiogenesis in an animal. The specification gives guidance for construction of said mutants, but the claims encompass any *in vivo* administration of said mutant, which may not necessarily reflect similar functioning even though the virus is administered. Therefore the statement of rejection indicates that the specification is enabled for an adenoviral virus comprising an E1 deletion comprising a mutation in the RB protein binding region of the conserved region 2 (CR2); for *in vitro* methods for substantially and selectively killing dividing cells and cancer cells with considerably less killing of quiescent or non-dividing cells in a mixed cell population comprising dividing endothelial or cancer cells and non-dividing or quiescent cells, by contacting the cell population with said mutant adenovirus; and for an *in vivo* method of tumor reduction by the intratumoral injection of the mutant virus of the instant invention. (Office action, dated 15 September 2000, paragraph bridging pages 5-6.)
>
> In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the lack of guidance set forth, the breadth of the claims, the quantity of experimentation required, one of skill in the art could not use the invention *in vivo* in any context without undue experimentation. (Office action, dated 15 September 2000, page 9.)

It is only in the context of *in vivo* administration that the Examiner asserted any support for this rejection in the literature by citing the teachings of the references of Dang, et al, (Clinical Cancer Research 5:471-474, Feb. 1999) and Eck, et al., (Goodman

& Gillman's *The Pharmaceutical Basis of Therapeutics*, Chapter 5 Gene Based Therapy, pages 77-101) and generically applying them to the areas of gene therapy and gene transfer *in vivo*. Subsequently, applicants have countered the references cited by the Examiner using references specific to the use of adenoviral vectors, which are the subject matter of the present invention.

Accordingly, in the first Office action the basis of the rejection of claims 1-24 under 35 U.S.C. §112, first paragraph, appeared to be focused on the assertion that "one of skill in the art could not use the invention *in vivo* in any context without undue experimentation." (Office action, dated 15 September 2000, page 9.)

In the second Office action, dated 6 June 2001, Examiner E. Sorbello maintained the rejection of claims 1-24 under 35 U.S.C. §112, first paragraph, for "reasons of record" (Office action, dated 6 June 2001, page 2). In the rejection the Examiner asserts the following:

> Applicants also directed examiner to numerous recent articles that applicants attest that the killing properties of adenoviruses have been taught, and therefore, applicants of the instant invention should be enabled for that which is claimed in the instant application. However, examiner contends that that is not the point in contention. The point that applicants are required to teach via *in vivo* examples is that in a cell population comprising dividing and quiescent cells, a method for substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells.
>
> In the absence of *in vivo* examples in an art accepted model in which applicants teach a method wherein dividing cells and not quiescent cells are infected with E1A-CR2 Rb binding site mutants, and wherein the dividing cells infected with the E1A-CR2 Rb binding site mutants are selectively and substantially killed, and not the quiescent cells, applicants are not enabled for that which they claim. (Office action, dated 6 June 2001, pages 3-4.)

Accordingly, in the second Office action the basis of the rejection of claims 1-24 under 35 U.S.C. §112, first paragraph, appeared to remain focused on the assertion that "one of skill in the art could not use the invention *in vivo* in any context without undue experimentation." (Office action, dated 15 September 2000, page 9.)

However, in the third Office action, dated 17 January 2002, Examiner E. Sorbello changes the rejection of claims 1-24 under 35 U.S.C. §112, first paragraph, to recite the following:

> Claims 1-24 remain rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for methods of substantially and selectively reducing tumor size by the intratumoral injection of Ad5 adenoviral vectors dl922/947 or dl1107 or pm 928, **does not** reasonably provide enablement for other limitations encompassed by the claims. (Underlining and bolding original, Office action, dated 17 January 2002, page 2).
>
> In support of the rejection the Examiner states the following:
>
> The unpredictable factors with regards to the site of injection for in vivo applications wherein adenoviral vectors carrying specific deletions are administered, are discussed in Office actions dated 9/15/00 and 6/5/01 remain for reasons of record. (Office action, dated 17 January 2002, page 2.)

However, in this rejection the Examiner has split the rejection into two components: first, limiting the adenoviral vectors to dl922/947 or dl1107 or pm 928; and second, limiting *in vivo* application to intramural injection. In this rejection the Examiner has **not** provided any basis for the limitation of the adenoviral vectors to the specific embodiments of dl922/947 or dl1107 or pm 928. In fact, this limitation is in contradiction of the Examiners statement, set forth in the first Office action, as follows:

> ...the statement of rejection indicates that the specification is enabled for an adenoviral virus comprising an E1 deletion comprising a mutation in the RB protein binding region of the conserved region 2 (CR2). (Office action, dated 15 September 2000, paragraph bridging pages 5-6.)

The shift in the rejection to limit the adenoviral vectors to dl922/947 or dl1107 or pm 928, is not support by any further evidence by the Examiner. The shift in the rejection limiting *in vivo* application to intramural injection is alleged to be supported by "the unpredictability factors" discussed in previous Office actions which appear to be generic application of the references of Dang, et al., and Eck, et al., to the areas of gene therapy and gene transfer *in vivo*.

In the final Office action, dated 20 April 2005, the Examiners have changed. The rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, is stated as follows:

> Claims 1-20 remain rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for methods of reducing the size of a tumor by intratumoral injection of the Ad5 vector disclosed as dl922/947, dl1107 or pm 928, does not reasonably provide enablement for the full scope of claims. The specification does not enable any person

> skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record. (Final Office action, dated 20 April 2005, page 2.)

Regarding the Examiner's asserted limitation of enablement to "the Ad5 vector disclosed as dl922/947, dl1107 or pm 928" applicants submit the following. First, limitation to these three specific adenovirus mutants is in direct contradiction to statement by first Examiner that "the statement of rejection indicates that the specification is enabled for an adenoviral virus comprising an E1 deletion comprising a mutation in the RB protein binding region of the conserved region 2 (CR2)" (Office action, dated 15 September 2000, paragraph bridging pages 5-6). Second, there are no Examiner arguments of record for this limitation and no evidence has been presented by the Examiner to support limiting the claims in this manner. Third, identification and characterization of adenoviral mutants (e.g., "a replication competent adenovirus comprising a mutation in the E1A RB family member binding region of said adenovirus," claim 1 of the present application) useful in the practice of the present invention are extensively discussed in the specification (see, for example: Figures 1-4, page 4; page 7, lines 15-19; page 8, line 25, to page 13, line 5; and pages 15-20). The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Applicants submit that one reasonably skilled in the art can make and use the adenoviral mutants of the present invention (e.g., "a replication competent adenovirus comprising a mutation in the E1A RB family member binding region of said adenovirus," claim 1 of the present application) without undue experimentation following the teachings of the specification.

Further, whenever the PTO makes such a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *See, In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). In the present case, regarding the limitation of

the claims by the Examiner to "the Ad5 vector disclosed as dl922/947, dl1107 or pm 928," the asserted rejection has (i) not been supported by acceptable evidence, and (ii) not been supported by reasoning to contradict the applicants' claim. In particular, the Examiner has presented no reasoning to buttress the rejection that is supported by the current literature as a whole. Accordingly, the Examiner has failed to prove that applicants' disclosure requires undue experimentation.

Regarding the Examiner's asserted limitation of enablement to "methods of reducing the size of a tumor by intratumoral injection" applicants submit the following. First, the Examiner's arguments are generic regarding the limitations of gene therapy and gene transfer *in vivo* and refer to only two publications for support (i.e., Dang, et al, and Eck, et al.). However, the applicants have rebutted these arguments with reference to the specification of the presently pending application, as well as by providing specific references in the field of oncolytic viruses to support their position, for example:

> Applicants respectfully submit that a reasonably skilled practitioner of this art would easily embrace Applicants' in vitro data to be predictive of the in vivo setting since in vitro model systems are routinely used in the field of oncolytic viruses to predict the in vivo killing properties of adenoviruses. The Examiner is referred to U.S. Patent No. 5,998,205 (Generic Therapeutics, Inc.) and U.S. Patent No. 5,698,443 (Calydon, Inc.). There are also many scientific publications that describe oncolytic adenoviruses and their killing properties. Two are: Journal of Virology, July 2000, page 6147, titled "Tumor-Specific Replication-Competent Adenovirus Vectors Overexpressing the Adenovirus Death Protein," and the Journal of Virology, March 2001, page 2857, titled "Replicating Adenoviruses that Target Tumors with Constituative Activation of the WNT Signaling Pathway." (Applicants' response, dated 17 July 2002, paragraph bridging pages 5-6.)

In the final Office action, dated 20 April 2005, the Examiner states the following:

> It is noted that Examples 3 and 4 (and all other Examples) have been fully considered as have the US Patents 5,998,205 and 5,698,443 and the two literature references cited. However, the instant specification, the Patents, and the cited references do not provide an enabling disclosure for the broad claims. (Final Office action, dated 20 April 2005, page 5).

Whenever the PTO makes such a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection

with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *See, In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). In the present case, regarding the limitation of the claims by the Examiner to "methods of reducing the size of a tumor by intratumoral injection" the asserted rejection has (i) not been supported by acceptable evidence, and (ii) not been supported by reasoning to contradict the applicants' claim. In particular, in view of the references provided by the applicants it cannot be said that the rejection asserted by the Examiner is supported by current literature as a whole. The Examiner has provided no evidence to rebut the teachings of the references referred to by the applicants nor has the Examiner provided any reasoning as to why the generic teachings of Deng, et al, and Eck, et al., support the Examiner's asserted rejection even in view of the teachings of the references provided by the applicants. Accordingly, the Examiner has failed to prove that applicants' disclosure requires undue experimentation.

Further, the Examiner is relying on improper standards for enablement of the claimed invention, for example:

> It is noted that **Example 4 does not indicate that intranasal inoculation can be used to effectively deliver the adenovirus to any tumor cell in the animal**, which is encompassed by the claims. With respect to Applicants' assertion that the Examiner is requiring that all of the data be from in vivo model systems, it should be made clear that the Examiner is not requiring all of the data to be in vivo data. **The Examiner is requiring the specification provide an enabling disclosure for the full scope encompassed by the claims.** (Bold emphasis added, underlining original, Final Office action, 20 April 2005, page 5.)

First, the Examiner's assertion that "Example 4 does not indicate that intranasal inoculation can be used to effectively deliver the adenovirus to **any** tumor cell in the animal" (emphasis added) reflects an improper standard of enablement. The standard for enablement is not that all possible species are exemplified and operable. Merely pointing out that a claim is broad, in that it reads on undisclosed as well as disclosed embodiments is not sufficient. The mere fact that a claim embraces undisclosed or possibly inoperative species or embodiments does not necessarily render it unduly broad. *See, Horton v. Stevens*, 7 USPQ2d 1245, 1247 (Fed. Cir. 1988).

Second, the Examiner's statement that "(t)he Examiner is requiring the specification provide an enabling disclosure for the full scope encompassed by the claims" also reflects an improper standard of enablement. The proper standard of enablement was set forth by the Board of Patent Appeals and Interferences as follows:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from **the disclosures in the patent coupled with information known in the art** without undue experimentation (emphasis added). *See, Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986).

In addition, although the Examiner has stated that the present rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, remain rejected "for the reasons of record" (Final Office action, dated 20 April 2005, page 2) this is clearly not the case. The reasons of recorded in the first office action recited the following:

> ...The point that applicants are required to teach via *in vivo* examples is that in a cell population comprising dividing and quiescent cells, a method for substantially and selectively killing dividing cells without the concomitant killing of non-dividing cells.
>
> In the absence of *in vivo* examples in an art accepted model in which applicants teach a method wherein dividing cells and not quiescent cells are infected with E1A-CR2 Rb binding site mutants, and wherein the dividing cells infected with the E1A-CR2 Rb binding site mutants are selectively and substantially killed, and not the quiescent cells, applicants are not enabled for that which they claim. (Office action, dated 6 June 2001, pages 3-4.)

In the final Office action, dated 20 April 2005, the Examiner stated the following:

> With respect to Applicants' assertion that the Examiner is requiring that all of the data be from in vivo model systems, it should be made clear that the Examiner is not requiring all of the data to be in vivo data. (Underlining original, Final Office action, 20 April 2005, page 5.)

In view of the contradictory nature of these two statements it is unfair for the Examiner to state that the reasons for the rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, are "of record." Accordingly, applicants submit that if the Examiner wishes to maintain the rejection of claims 1-20 under 35 U.S.C. §112, first paragraph, the basis of the rejection must be clearly set forth and not simply deferred by reference to "reasons of record."

Finally, in support of the specification providing enablement for the full scope of the claims, applicants set forth the following in the response dated 17 July 2002:

> On page 7, lines 21-22 the Examiner will note that the Applicants contemplated modes of administration other than intratumoral. For example, there Applicants state that "Standard techniques are used...pharmaceutical formulation and delivery, and treatment of patients." Clearly, a skilled practitioner of this art would understand that Applicants intend that standard modes of administering adenovirus include systemic administration which could be achieved by a number of means, including intravenous injection.
>
> Moreover, the Examiner will further note that Applicants have incorporated by reference U. S. Patent No. 5,6,77,178 in its entireity. Column 17, lines 1-20, states:
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> > A adenovirus suspension containing about 10.sup.3 to 10.sup.12 or more virion particles per ml may be inhaled as a mist (e.g., for pulmonary delivery to treat bronchogenic carcinoma, small-cell lung carcinoma, non-small cell lung carcinoma, lung adenocarcinoma, or laryngeal cancer) or swabbed directly on a tumor site for treating a tumor (e.g., bronchogenic carcinoma, nasopharyngeal carcinoma, laryngeal carcinoma, cervical carcinoma) or may be administered by infusion (e.g., into the peritoneal cavity for treating ovarian cancer, into the portal vein for treating hepatocarcinoma or liver metastases from other non-hepatic primary tumors) or other suitable route, including direct injection into a tumor mass (e.g., a breast tumor), enema (e.g., colon cancer), or catheter (e.g., bladdercancer).
>
> Incorporation of this patent, with the relevant section presented above, clearly supports other modes of administering adenovirus in addition to intratumoral rejection. (Response, dated 17 July 2002, page 3.)

In response to this argument, the Examiner stated the following in the final Office action:

> With respect to Applicants arguments that the specification has disclosed routes of administration other than intratumoral delivery, **it is acknowledged that the specification has disclosed the other routes of administration.** The question is whether or not the specification has an enabling disclosure for the full scope of the claims. It is noted that Applicants acknowledge that the claims encompass systemic administration. However, the specification does [*sic*] provide an enabling disclosure for systemic administration or for any other administration other than an administration that would result in the direct delivery of the adenovirus to the tumor cells. Therefore, Applicants arguments that the

> specification discloses different routes of administration is not persuasive because the specification has not enabled the routes of administration other than direct delivery.
>
> With respect to Applicants arguments regarding the disclosure of the '178 patent, it is acknowledged that the '178 patent discloses the indicated routes of administration. However, the '178 patent **does not provide an enabling disclosure for the any route of administration other than direct delivery to the tumor cells.** Therefore, Applicants arguments regarding the disclosure of the '178 patent are not persuasive. (Emphasis added, final Office action, dated 20 July 2005.)

The Examiner has "acknowledged that the specification has disclosed the other routes of administration." However, the Examiner discounts applicants' argument that U.S. Patent No. 5,677,178 clearly supports other modes of administering adenovirus in addition to intratumoral rejection. The Examiner's argument regarding U.S. Patent No. 5,677,178 is completely improper. The Examiner is reading a limitation into the issued claims of U.S. Patent No. 5,677,178 that is not present in the claims, that is, "the '178 patent **does not provide an enabling disclosure for the any route of administration other than direct delivery to the tumor cells**" (Emphasis added, final Office action, dated 20 July 2005). For example, independent claim 15 of U.S. Patent No. 5,677,178 is as follows:

> 15. A method for treating a neoplastic condition in a human, comprising administering a composition comprising a therapeutically effective dosage of recombinant replication deficient adenovirus to a human patient having a neoplasm comprising neoplastic cells lacking a functional p53 tumor suppressor gene product.

Applicants remind the Examiner that every patent is presumed to be valid (35 U.S.C. §282, first sentence). The Examiner's statement regarding the enablement of the disclosure of U.S. Patent No. 5,677,178 may be interpreted to imply a limitation not found in the claims of the patent. Thus, the Examiner's comment may be construed to reflect on the validity of U.S. Patent No. 5,677,178. MPEP 1701 (Eighth Edition) states the following (emphasis added):

> Every patent is presumed to be valid. 35 U.S.C. 282, first sentence. **Public policy demands that every employee of the United States Patent and Trademark Office (USPTO) refuse to express to any person any opinion as to the validity or invalidity of, or the patentability or unpatentability of any claim in any U.S. patent**, except to the extent

necessary to carry out
(A) an examination of a reissue application of the patent,
(B) a reexamination proceeding to reexamine the patent, or
(C) an interference involving the patent.
The question of validity or invalidity is otherwise exclusively a matter to be determined by a court.

Accordingly, applicants respectfully request that the Examiner withdraw the comments directed to the scope of enablement of U.S. Patent No. 5,677,178 as the claims in that patent have issued and are entitled to a presumption of validity. Further, as previously stated by the applicants, U.S. Patent No. 5,677,178 (which was incorporated by reference in the present application) clearly supports other modes of administering adenovirus in addition to intratumoral rejection. The Examiner has not supported the asserted reasons for the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: such reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *See, In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

In addition, U.S. Patent No. 6,080,578, cited by the Examiner in the rejection asserted under 35 U.S.C. §102(e) teaches the efficacy of systemic administration (i.e., intravenous administration) of replication-deficient recombinant adenovirus for tumor cell killing (see, e.g., cols. 22-23). The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Accordingly, the Examiner has provided no evidence to rebut the objective enablement of applicants' specification for routes of administration including, for example, systemic administration.

In conclusion, applicants have provided enablement for the scope of the claims. Applicants submit that the Examiner has failed to provide (i) acceptable evidence, or (ii) reasoning supported by current literature as a whole that contradicts the applicants' claim. *See, In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI International v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 227 USPQ 577 (Fed. Cir. 1985). Further, the enablement requirement

may be satisfied even though some experimentation is required. *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 231 USPQ 81 (Fed. Cir. 1986). Applicants submit that if the Examiner intends to maintain the rejection of claims 1-20, under 35 U.S.C. §112, first paragraph, then the rejection must be clarified in view of the inconsistencies discussed herein above and conform with the established standards for the enablement requirement, also discussed herein above.

In view of the above arguments applicants submit that the claims comply with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, withdrawal of the rejection of claims 1-20, under 35 U.S.C. §112, first paragraph, is respectfully requested.

III. Rejection of Claims 1-6 Under 35 U.S.C. §102(e).

The Examiner maintained the rejection of claims 1-6 under 35 U.S.C. §102(e) asserting that the claims are anticipated by Bischoff, et al. (U.S. Patent No. 6,080,578).

For prior art to anticipate under 35 U.S.C. §102 it has to meet every element of the claimed invention: such a determination is one of fact. *See, Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 231 USPQ 81 (Fed. Cir. 1986).

In the final Office action, dated 20 April 2005, the Examiner asserts the following:

> With respect to Applicants' arguments that claim 1 has been amended to recite that the dividing cells consist of cancer cells and endothelial cells, it is respectfully pointed out that claim 1 specifically recites, "In a cell population comprising dividing and quiescent cells, wherein said dividing cells comprise cancer and endothelial cells, a method ... comprising contacting said cell population...with a replication competent adenovirus comprising a mutation in the E1A RB family member binding region of said adenovirus...". Given the broadest reasonable interpretation, "a cell population comprising dividing and quiescent cells" encompasses an animal as animals cell populations comprising dividing and quiescent cells. Therefore, given the broadest reasonable interpretation, the claims encompass a method wherein the mutant adenovirus is "contacted with" an animal comprising dividing cancer and endothelial cells. Bishoff teaches administering treating cancer by administering a mutant adenovirus encompassed by the claims to the cancer cells wherein the cancer cells are in an animal (e.g., see column 10, lines 10-42; column 16, lines 18-67; column 17, lines 1-35; column 18, line 30 through column 19, line 56, etc.). Therefore, Bischoff does teach the limitations of the instant claims. (Final Office action, dated 20 April 2005, pages 6-7.)

Applicants respectfully submit that the Examiner's "broadest reasonable interpretation" of the claims is in error. The language of pending claim 1 is as follows:

> In a cell population comprising dividing and quiescent cells, wherein said dividing cells comprise cancer and endothelial cells, **a method for substantially and selectively killing said dividing cells**, said method comprising contacting said cell population under infective conditions with a replication competent adenovirus comprising a mutation in the E1A RB family member binding region of said adenovirus, and allowing sufficient time for said adenovirus to infect said cell population. (Emphasis added.)

Applicants submit that the cited references do not teach all of the elements of the present invention because the reference of Bischoff, et al., does not teach the substantial and selective killing of dividing cancer **and endothelial cells**. As the Examiner has pointed out the language of pending claim 1 recites "wherein said dividing cells comprise cancer and endothelial cells." The claim also recites that it is directed to "a method for substantially and selectively killing said dividing cells." According to MPEP 2111.03 (Eighth Edition):

> The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. See, e.g., >*Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003) ("The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps.");< *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997) (**"Comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.**); *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). (Emphasis added.)

Accordingly, in view of the guidance of MPEP 2111.03, because the language of the claims recites "wherein said dividing cells comprise cancer **and** endothelial cells," then the substantial and selective killing of the dividing cells includes the substantial and selective killing of cancer **and** endothelial cells, that is, the method of the present

invention for substantially and selectively killing dividing cells comprising cancer and endothelial cells means the substantial and selective killing of the named elements (i.e., cancer and endothelial cells) are essential, but other elements may be added.

The reference of Bischoff, et al., contains no teaching directed to the substantial and selective killing of dividing endothelial cells. Accordingly, the reference of Bischoff, et al., does not anticipate the invention of claims 1-6.

It is an important feature of the methods and compositions of the present invention that they are useful for "substantially and selectively ablating cancer cells and dividing endothelial cells while substantially sparing quiescent normal cells" (Abstract). This feature is described throughout the specification (see, for example, page 9, line 22, to page 10, line 3; page 10, lines 18-25; and page 12, lines 10-15).

In view of the above arguments, applicants submit that the cited references do not teach all the elements of the present invention. Accordingly, applicant respectfully requests withdrawal of the rejection of the claims under 35 U.S.C. §102(e).

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502.

Respectfully submitted,

Date: 20 June 2005 By: Gary R Fabian

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